

to correct dependency. Claim 11 has been amended to additionally define the subject invention. Support for the amendment is discussed hereunder.

The 35 U.S.C. §112, First Paragraph, Rejections

Claims 11 and 12 stand rejected as there is allegedly insufficient exemplary matter to support item (1) and item (2)B-G and I. Withdrawal of the rejection is believed to be in order for the reasons that follow.

Claim 11, item (1) has been amended to recite a ratio of antithrombotic activity to anticoagulant activity of about 2.5. Support for the amendment is found in the specification on page 8, lines 28 and 29. One of ordinary skill in the art, on reading the specification, would appreciate that the value 2.5 was the result of the experiment described and that repetitive tests would result in ratios of approximately that range. Thus, it is submitted that to require limitation of item (1) of claim 11 to specifically 2.5 would be unduly restricting Applicants in the scope to which they are rightfully entitled. The same argument applies to use of "about" in item (2) F and G of claim 11. The use of the word "about" in item (2) B-D and I, as now presented, finds support in claim 8 as originally filed wherein statistical variation is indicated.

In view of the foregoing amendments and comments, it is respectfully submitted that the claims as presented are commensurate in scope with the enablement provided by the subject disclosure. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The 35 U.S.C. §112, Second Paragraph Rejections

Claims 11 and 12 stand rejected as allegedly being indefinite. Withdrawal of the rejection is believed to be in order for the reasons that follow.

Claim 11 has been amended to recite the specific tests used to measure both antithrombotic and anticoagulant activity. The amendment is believed to obviate the Examiner's rejection; withdrawal of the rejection is therefore requested.

The 35 U.S.C. §102 Rejections

Claims 1-7 and 10-12 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Thrombosis Research. Applicants respectfully traverse the rejection for the reasons that follow.

The Examiner indicates on page 3 of the Action that the low molecular weight heparin fractions disclosed in the references appear to fall within the upper range of the claims. By the Examiner's own admission, one cannot determine with certainty that an oligoheteropolysaccharide comprising a heparin fraction having the claimed molecular weight and quantity and position of active groups is disclosed. As the Examiner is aware, if a reference is ambiguous and can be interpreted so that it may not constitute any anticipation of Applicants' claims, a rejection of the claims as anticipated is improper (In re Brink 164, U.S.P.Q. 247 (1970)). Accordingly, Applicants submit that the rejection based on anticipation should be withdrawn. Applicants also direct the Examiner's attention to the fact that the 2 later Thrombosis Research references (1977 and 1978) were published after the filing date of the priority application and

thus cannot be cited against the present application.

The 35 U.S.C. §103 Rejections

Claims 1-7 and 10-12 stand rejected as allegedly being unpatentable over British patent 674,607 and Hladovec et al in view of Nader et al, Waldman et al, and Thrombosis. Applicants respectfully traverse the rejection for the reasons that follow.

British patent 674,607 relates to the sulfation of by-products of heparin manufacture, which sulfated products display blood anticoagulant activity. The object of the British patent is to provide blood anticoagulants having an activity approximating that of pure heparin (see page 2, lines 38-44). In contrast, it is the object of the present invention to provide a product, the therapeutic action of which is modified in order to improve the antithrombotic action in preference to the anticoagulant action. Since the British patent makes no mention of the antithrombotic activity of the product disclosed therein, one of ordinary skill in the art on reading the British patent, would have no basis for concluding that Applicants claimed compound could be obtained by the same method. If any guidance were offered the teachings of the British patent, it would be that the process of the British patent was not a suitable method for solving the problem to which Applicants' invention is directed.

Haldovec et al. relates a method of preparing heparinoids, including a sulfonated ovomucoid, a sulfonated hyalomucoid, a sulfonated amylose depolymerized and partially depolymerized, a sulfonated saponin and a sulfonated tannin. The reference discloses the antilipemic and anticoagulant activities of each of the substances relative to heparin. Hladovec et al.

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103 reject

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discloses that sulfonated ovomucoid, sulfonated hyalomucoid and sulfonated amylose undepolymerized, display little antilipemic activity but relatively high anticoagulant activity. The reference does not address the question of antithrombotic activity displayed by the compounds and thus, could not render obvious Applicants' claimed invention. Furthermore, the reference adds nothing to the teachings of the British patent which would bring one skilled in the art closer to Applicants' claimed invention.

The Examiner cites Nader et al., Waldman et al. and Thrombosis as secondary references.

Nader et al. examined the effect of heparitin sulfate fractions on coagulation and hemostasis compared to heparin. The citation makes no mention of antithrombotic activity.

Waldman et al. disclose the effect of N-sulfate and O-sulfate groups on the ability of heparin to inhibit protein synthesis and to prevent coagulation. The data presented demonstrate that the ability of heparin to inhibit initiation of translation of messenger RNA and to inhibit coagulation have significantly different dependencies on the degree of N-sulfation. Like Nader et al., Waldman does not address the question of the effect of sulfation on antithrombotic activity.

Since, as noted above, two of the Thrombosis Research references have been improperly cited, only the relevant citation (1976) will be discussed. On page 580 of the citation, it is indicated in Figure 2 that the ratio of anti-X_a to APTT of a commercial preparation of heparin having a molecular weight of 5,000 is approximately 20, the APTT value being only approximately 4.5 units/mg. The reference provides no indication as to the nature of the low molecular weight fraction, much less the state

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of sulfation of the same.

Thus, Applicants submit that the cited references, taken alone or in combination, neither teach nor suggest the essential features of the presently claimed invention. Accordingly, withdrawal of the rejection is earnestly solicited.

In view of the foregoing, it is respectfully submitted that all of Applicants' claims are in acceptable form and define patentable invention over the art of record. Accordingly, reconsideration is requested.

Respectfully submitted,
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